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Nocardia nova as the Causative Agent in Spondylodiscitis and Psoas Abscess▽

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We describe here the first case of *Nocardia nova* spondylodiscitis accompanied by a psoas abscess due to spreading from pulmonary nocardiosis. *Nocardia* was cultured from all affected sites. After 1 year of an appropriate antimicrobial therapy and a surgical drainage of the abscess that was required, the patient's clinical condition had improved.

CASE REPORT

In 2001, a 27-year-old female was admitted to the Department of Nephrology-Transplantation Section because of abdominal and back pain, accompanied by a high-grade fever. In 1991, she was diagnosed with end-stage renal disease due to focal segmental glomerular sclerosis. She was treated for 1 year using hemodialysis, and in 1992 she received her first renal cadaveric transplant, but it was rejected 1 year later. In March 2000, she received a second renal transplant. Because of several episodes of acute rejection despite treatment with prednisone, cyclosporine, and mycophenolate mofetil, the hemodialysis was restarted 6 months later, and the graft was removed. After this surgery, she developed *Staphylococcus epidermidis* septicemia and an *Aspergillus fumigatus* pulmonary infection. Immunosuppressive therapy was discontinued and, despite antimicrobial therapy directed against these two infections, 1 month later (October 2000) she developed a second pulmonary infection with high fever, nonproductive cough, and dyspnea. A chest X-ray and computed tomography showed multiple nodules without cavitations.

Bronchial aspirate, bronchoalveolar lavage fluid, and a lung biopsy analyses were performed. Direct Gram-stained smears of all specimens showed branched gram-positive rods, and a modified acid-fast stain was positive. Cultures of all specimens grew a *Nocardia* species. Growth on blood agar and chocolate plates occurred within 3 days of inoculation and showed white opaque and dry colonies, which became chalky and orange with prolonged incubation. The presumptive diagnosis as *Nocardia nova* complex was obtained from a combination of growth characteristics, aerial hypha production, lysozyme resistance, and a drug susceptibility test performed by the disk diffusion method (5, 20).

The patient became afebrile 7 days after the start of a 6-week treatment with intravenous antibiotics, including amikacin (500 mg once daily), imipenem (500 mg three times daily), and trimethoprim-sulfamethoxazole (80 mg of trimethoprim and 400 mg of sulfamethoxazole; two vials of 5 ml administered twice daily), followed by 2 months with the latter two antibiotics alone. Her clinical condition improved rapidly. She was discharged from the hospital and was treated by hemodialysis three times a week.

In August 2001, she complained of abdominal and back pain and progressive fever. Her temperature was above 39°C with a normal physical examination except that her back was painful, with the pain was exacerbated when she moved. The spine was tender to palpation at the level of L4-L5 without neurological signs.

The laboratory evaluation showed an elevated C-reactive protein (CRP) level of 115 mg/liter and leukocytes at 120,00/mm^3. All blood cultures were negative for bacterial growth. Abdominal ultrasonography revealed a noncomplicated left ovarian cyst, and ^{99m}Tc scintigraphy of the skeleton indicated an increased signal at the L4-L5 position. Subsequently, a magnetic resonance imaging scan of the lumbar spine confirmed increased signal intensity in the same location compatible with the diagnosis of spondylodiscitis at L4-L5 (Fig. 1 and 2) and revealed a psoas abscess.

A CT-guided needle aspiration of the affected vertebra was performed. No organisms were seen on a Gram-stained smear of the specimen. The aspirate of the affected vertebra was inoculated onto blood agar and chocolate plates that were incubated in a CO_2-enriched atmosphere at 37°C for 10 days and was reported as negative. The specimen was also processed through BacT/Alert broth medium (bioMérieux, Marcy l'Etoile, France) which was incubated for 4 weeks in aerobic condition because of the previously pulmonary nocardiosis. The recovery of the organism from the BacT/Alert broth confirmed the presence of nocardiae at this site.

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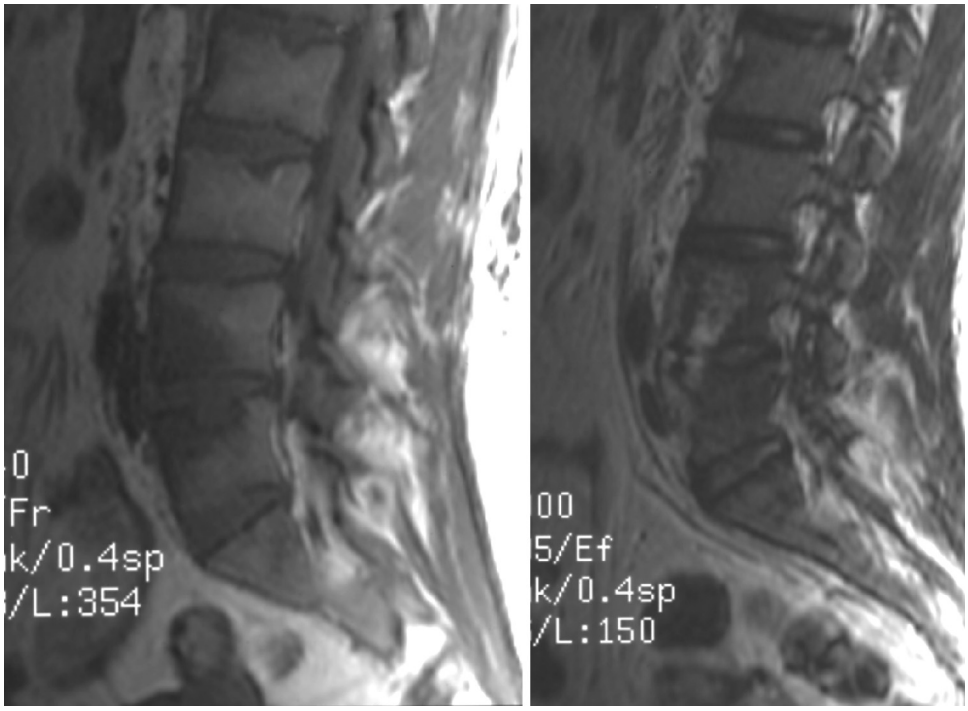

FIG. 1. Magnetic resonance imaging scan of the lumbar spine revealed an increased signal at position L4-L5.

Antimicrobial treatment with amikacin, imipenem, and cotrimoxazole was restarted. No other localization of the disease was found at this time.

One month later, the amikacin treatment was stopped despite a temperature higher than 39°C and an increased CRP level above 200 mg/liter after each hemodialysis session. Amoxicillin (2 g given three times daily by the oral route) was started.

In October 2001, a new CT scan revealed a voluminous psoas abscess (Fig. 2). It was drained surgically under tomographic guidance.

A Gram stain of the evacuated pus showed a branched-positive rod, and a modified acid-fast stain was positive for organisms morphologically consistent with *Nocardia* species. Bacteriologic culture grew a *Nocardia* species.

The lumbar pain improved, the patient became afebrile, and the CRP level decreased to 30 mg/liter 2 weeks after drainage. Imipenem was switched to erythromycin (1 g given three times daily by the oral route) because of adverse side effects (a seizure). Again, the CRP level began to increase, and another CT scan was performed. The abscess had increased in size, so open surgery was performed to drain the psoas abscess. After the surgical procedure and a 1-year treatment with oral erythromycin and amoxicillin, the patient's clinical condition had improved.

The *Nocardia* isolates were referred to the Nocardiosis French Observatory, where they were subsequently identified as *N. nova* by biochemical testing, including a positive 2-week arylsulfatase assay and the negative decomposition of casein, xanthine, tyrosine, and hypoxanthine. Accurate species identification was determined by sequencing the 5′-end 606-bp frag-

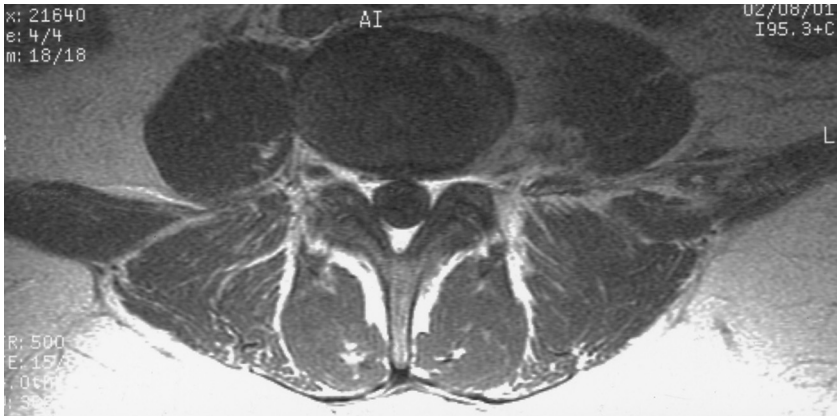

FIG. 2. Computed tomography scan of the chest showing voluminous psoas abscess.

ment of the 16S rRNA gene and concluded to be *N. nova* sensu stricto. The gene was amplified as previously described (15) with the primers Noc1 (5′-GCTTAACACATGCAAGTCG-3′; positions 46 to 64 [*Escherichia coli* numbering system]) and Noc2 (5′-GAATTCCAGTCTCCCCTG-3′; position 663 to 680 [*E. coli* numbering system]), and the sequencing gene was based on the search of the phylogenetically closest known species inferred from the Nocardiosis French Observatory database. This database included 16S rRNA sequences from reference strains of all validated nocardial species. The database comparison, using Bibi software (7), generated a list of the closest matches with pairwise distance scores indicating the percent difference between the unknown sequence and the database sequences. The three strains that were recovered from our patient formed a phylogenetic individualized cluster with *N. nova* ATCC 33726T (data not shown) and showed 100% similarity to the type strain.

Comparison of the relapse isolates with the agent from the primary pulmonary infection was performed by randomly amplified polymorphic DNA analysis, using the DKU49 (5′-CCG CCGACCGAG-3′) primer as previously described (13). This procedure established that the isolates from the second and the third samples were of the same genotype as the first isolate.

At this time, there has been no recurrence of the infection even though the patient remained on hemodialysis. Clinical follow-up evaluation has continued regularly.

The nocardiae are infrequently recognized to cause clinical disease in normal patients, but they are more frequently diagnosed as causing disease in immunocompromised patients. The predisposing factors are long-term corticosteroid therapy, chronic lung disease, hematologic and other malignancies, and organ transplantation. Renal transplant recipients are a subgroup of immunocompromised patients for whom *Nocardia* is an important cause of morbidity and mortality, and the prevalence of nocardiosis has been reported to be as high as 5% (9, 22). Risk factors for nocardiosis in renal transplant recipients include multiple early rejection, intensive immunosuppressive therapy, and granulocytopenia (1). Recently, mycophenolate compounds, which block the proliferation of T and B cells, inhibit antibody formation, and prevent the generation of cytotoxic T cells, have been implicated as predisposing factors for nocardial infection (11, 14). Our patient had all of these predisposing factors.

Pulmonary nocardiosis is a primary clinical finding that may be either self-limited or subclinical. It may progress to an acute, subacute, or chronic process mimicking tuberculous, mycotic infections or a neoplasm (10). Once blood-borne, the organisms can invade other anatomic locations, with the frequency of disseminated disease ranging between 28 and 56% (17, 19). The most common sites for dissemination are the central nervous system, skin and subcutaneous tissues, eyes (especially the retina), kidneys, joints, and the heart (12). Osteomyelitis due to nocardiae is uncommon. Only 12 cases of *Nocardia* osteomyelitis of the spine have been published over the past 40 years, and 4 of these were located at lumbar sites (8).

The clinical diagnosis of nocardiosis is difficult. Signs, symptoms, and radiology are not pathognomonic. However, due to the nature and gravity of nocardiosis, rapid and precise identification of these agents is important. In routine clinical laboratories, the evaluation of appropriate specimens by smear and culture remains the principal method of diagnosis. Phenotypic characteristics are often used in conjunction with antimicrobial susceptibility patterns to help identify some nocardial isolates (4, 5, 6, 18, 21). *N. nova* complex has a distinct antimicrobial susceptibility pattern; the species of this complex are susceptible or moderately susceptible to both amoxicillin and erythromycin and resistant to both amoxicillin-clavulanic acid and tobramycin (5, 6, 18, 20). Although phenotypic methods and susceptibility patterns are used for identification, they are not reliable as definitive identification methods. Gene sequencing provides a more reliable identification, and the 16S rRNA gene sequence has become the new gold standard (3).

Accurate strain identification is essential for defining the spectrum of disease caused by each species, for predicting antimicrobial susceptibility, and for general comparisons of clinical isolates for epidemiological reasons.

Nocardiosis is also often difficult to treat and can be guided by susceptibility testing. Early and prolonged treatment with a combination of antibiotics is necessary in order to avoid either recurrence of infection, metastatic spread, or drug resistance. Even though cotrimoxazole remains the drug of choice for the treatment of nocardiosis, combinations with imipenem and amikacin have been utilized successfully (10, 16).

N. nova is characterized by susceptibility to amoxicillin and erythromycin, and combination of these drugs offers a potential oral therapy for patients with nocardial infection (10).

The duration of therapy for nocardiosis is uncertain, but it should be protracted because of the high incidence of relapse after shorter courses of therapy (2).

The spondylodiscitis and psoas abscess reported here followed dissemination from the lung, which was the primary site of nocardial infection. *Staphylococcus aureus* remains the etiologic agent most commonly identified in patients with spondylodiscitis and psoas abscess. Nevertheless, a wide variety of other etiologic agents have been identified, such as *E. coli* and *Proteus mirabilis*. Nocardiae as the causative agent of spondylodiscitis and psoas abscess is an uncommon finding. No case of disseminated *N. nova* osteomyelitis has been reported in the English literature even though dissemination is especially prevalent with *N. farcinica* (16).

The fact that the bacteriologic etiology of this spondylodiscitis was not obtained by direct culture of the aspirate of the affected vertebra onto blood agar and chocolate plates may be due to the very low level of bacteria at this site. *Nocardia* species was detected at this site by using the BacT/Alert system and when the sample was subcultured late (after 4 weeks of incubation) onto blood agar medium. Thus, we recommend processing the sample through the Bact/Alert system or a similar system so as to increase the growth sensitivity of the nocardiae.

Once the diagnosis of pulmonary nocardiosis was made, the patient described here received 3 months of antimicrobial therapy that included imipenem, amikacin, and cotrimoxazole for pulmonary nocardiosis. Obviously, this duration was insufficient, explaining the spread of the disease 8 months after the discontinuation of the therapy.

Treatment of the spondylodiscitis and the psoas abscess with cotrimoxazole, imipenem, and amikacin did not result in clinical improvement, probably because the antibiotics could not adequately reach the *Nocardia* through the thick layer of pus present in the psoas abscess. For this reason, surgical drainage was necessary.

In conclusion, the microbiological diagnosis is not difficult if clinician and clinical microbiologist are aware of the possibility of nocardiosis.

Long-term antibiotic therapy for 6 months to a year or longer (8, 12) is needed to treat *Nocardia* due both to the slow replication rate of the organisms and to its ability to become an intracellular pathogen that can persist as a cryptic form in the host. In addition, in patients with abscesses, surgical drainage may be required in order to ensure adequate penetration of antibiotics and clearance of the bacteria.

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